WORKSHOP ON MONITORING HIV RESISTANCE TO ARV DRUGS IN THE AFRICAN REGION

REPORT

Johannesburg 10 - 12 April 2002

REGIONAL PROGRAMME ON HIV/AIDS
WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR AFRICA

ABBREVIATIONS

1. ACD	Acid citrate dextrose
2. ARV	Antiretroviral
3. AZT	Zidovudine
4. CDC	Centres for Disease Control
5. CDC ARVDR	Centres for Disease Control Antiretroviral Drug Resistance
6. CD4	Lymphocyte T4
7. CIPLA	Pharmaceutical Laboratory Company
8. CRFs	Circulating Recombinant Forms
9. CWRU	Case Western Reserve University Cleveland
10. EDTA	Acid ethylen diamine tetra acetic
11. HAART	Higly Active Antiretroviral Treatment
12. HIV	Human Immunodefiency Virus
13. HIV1	Human Immunodefiency virus 1
14. IAS	International AIDS Society
15. JCRC	Joint Clinical Research Centre
16. MTCT	Mother to Child Transmission
17. NGOs	Non Governmental Organisation
18. NRTI	Non-Reverse Transcriptase Inhibitor
19. NVP	Nevirapine
20. PCR	Polymerase Chain Reaction
21. PEP	Post-Exposure Prophylaxis
22. PI	Protease Inhibitor
23. QA	Quality Assurance
24. RNA	Ribonucleic Acid
25. STARHS	Serological Testing Algorithm for Recent HIV Seroconversions

26.	TB	Tuberculosis
27.	UNAIDS	Joint United Nations Programme on HIV/AIDS
28.	WHO	World Health Organisation
29.	WHO/AFRO	World Health Organisation Regional Office for Africa
30.	ZDV	Zidovudive
31.	3TC	Lamivudine

1.0 INTRODUCTION:

The genetic heterogeneity of HIV1 isolates is one of the major characteristics of the virus and the epidemic. This diversity, generated by the processes of mutation and recombination, has led to the development of a subtype nomenclature for the classification of isolates. The major (M) group of HIV-1, responsible for the majority of infections in the epidemic, contains several types, and at least 10 circulating recombinant forms (CRFs). In addition the extraordinarily rapid rate of HIV-1 evolution in humans, estimated at around 0.0024 substitutions per base pair per year, coupled with the recombination events that may introduce large-scale genetic changes creates the conditions for increased viral evolution.

The high level of genetic diversity of HIV-1, coupled with the fast turnover of virions, has been shown to lead to the rapid generation of drug-resistant strains. Mutations conferring resistance to antiretroviral drugs have been described in drug-naïve patients with variable prevalence by countries. The transmission of resistant variants to uninfected individuals raises serious clinical and public health consequences, as it may compromise the response to initial therapy. There is therefore the need to evaluate the prevalence of circulating resistant HIV strains.

The surveillance of drug resistance in a community of both naive and treated HIV infected individuals will provide useful information for the design of preferred drug combinations. The review of the situation in some African countries shows different levels of resistance to some drugs (Zidovidine, Indinavir, Lamivudine, Neverapine, Saquinavir, Ritonavir, etc).

WHO, in pursuance of its technical role, needs to consolidate and disseminate information on the prevalence of HIV resistant strains to countries to facilitate the development of appropriate policies. This has become more relevant with the implementation of the WHO Access to Care Initiative, including ARV. WHO has to provide technical leadership in detecting HIV resistance through a network of laboratories. Toward this end, WHO /AFRO seeks to establish a partnership with laboratories in the region that already have the human and technical capacity in this area. To this end WHO organized a workshop in Johannesburg, South Africa from 10 – 12 April 2002. The workshop brought together experts from selected laboratories to develop a protocol for monitoring HIV resistance to ARV.

The meeting was opened by Dr Shasha, WHO liaison officer, South Africa.

2.0 OBJECTIVES AND EXPECTED OUTCOMES:

- **General objective:**

To strengthen monitoring of HIV resistance to ARV drugs in order to guide effective and safe use of ARV in the African Region.

- **Specific objectives:**

The specific objectives were:

- To document existing practice in monitoring HIV resistance to ARV drugs in the African region.

- To finalize and agree on a protocol for monitoring HIV resistance to ARV drugs in the African region.
- To define the role of the participating laboratories in monitoring HIV resistance to ARV drugs in the African region.
- To agree on the next steps for monitoring HIV resistance to ARV drugs.

3.0 PROCEEDINGS:

3.1 Regional overview on HIV resistance.

It is estimated that there are 40 million people currently living with HIV globally of whom 28 million reside in Africa. The burden of infection is not uniformly distributed with the heaviest burden in Southern Africa, followed by Central and East Africa and the lowest burden in West Africa. There is also an unequal distribution of subtypes with C more predominant in Southern Africa; A, C, and D in East and Central Africa; with A and A/G dominating in West Africa .

Unlike 3-4 years ago, access to anti-retroviral drugs is becoming a real possibility in Africa. This is largely the result of price reductions as well as the development of generic drugs. This is an important breakthrough for the region. However, along with accessibility come many challenges of which ARV resistance is one of them. WHO has made drug resistance to ARV a priority activity as part of integration of the global initiative.

The prevalence of ARV resistance in drug naïve patients in Africa is unknown. While newly infected individuals provide the best data on spread of resistant mutants, and thus the best information for choosing ARV therapy over time, these individuals are difficult to identify and enroll, and are poorly representative of all HIV infections. Newly diagnosed individuals, although easy to enroll, and possibly more representative, may change resistant patterns with duration of infection. Screening for transmission of drug-resistant viruses is important to enable countries to optimise drug selection, minimize costs and assist public health decision-making.

3.2 Safe And Effective Use Of ARV - Issues And Challenges:

It is estimated that over 90 % of individuals in Africa do not know their HIV serostatus, and that most health facilities lack capacity for diagnosis and treatment of HIV/AIDS patients. Although the use of ARV in the African region dates back to the mid and late 1990s, the numbers of individuals on ARVs in Africa are restricted to only a few – it is estimated that 20 000 HIV patients are on ARVs. Use of ARV is happening in the background of lack of well-formulated ARV policies or technical guidelines. In addition, health staff is not trained on ARV use and laboratories are not equipped to support monitoring of ARV treatment. This will result in variable regimes, which will contribute to the development of resistance to a number of ARVs.

An acute awareness of the magnitude of the problem in Africa has led to intense advocacy and resource mobilization such as the Global Fund to Fight AIDS, TB and Malaria. In the preparation of documents on recommended drug regimes for first, second and third line treatment, a critical look at safety and effective use needs to be done. In addition procurement and supply systems need to be strengthened. In conjunction with this, countries need adequately trained health providers, correct supervision of patients on ARVs to ensure adherence to treatment, careful counseling on treatment.

3.3 Country Presentations:

Country presentations were from Côte d'Ivoire, Uganda and South Africa. Below is a summary of the situation of each of the countries.

ARV Drug Resistance in Côte d'Ivoire

An ARV drug programme was initiated in 1998 in Cote d'Ivoire through a UNAIDS initiative, with monitoring provided by CDC. Studies currently underway in Abidjan aim to determine the prevalence of:

- Genotypic ARV drug resistance in naïve HIV-1 infected pregnant women receiving short course ZDV
- Baseline polymorphism among HIV-1 infected drug naive patients
- Genotypic and drug resistance among patients with a prior history of ARV
- Genotypic and phenotypic drug resistance among HIV-1 infected patients with rebound viral loads
- To determine virologic, immunologic response and genotypic resistance.

In addition, studies are underway investigating the effectiveness of certain drugs in HIV-2 infected individuals, as well as to type drug resistant mutations in HIV-2 infection. Clinical guidelines are being developed for clinical and biologic follow-up of patients.

ARV Drug Resistance in UGANDA

Uganda has been pioneering the use of ARV therapy since 1992, with Protease Inhibitors (PI) used since 1996. From Oct. 2000, Uganda started importing generic ARVs from CIPLA, India, and there have been subsequent dramatic reductions in brand drugs. Due to increased affordability the number of, patients on HAART has increased from 100 in 1996 to 3 500 by Feb 2002. The opening up of UNAIDS accredited centres for HIV drug access initiative introduced in 1998 also resulted in increased access. Currently, patients pay for drugs and monitoring although the government has programs to increase access through NGOs. Recently up-country centres have been opened (outside of Kampala). There are also MTCT plus projects.

Resistance screening is being done by groups at JCRC, CDC, Johns Hopkins and CWRU. The objectives of these studies are to:

- Determine the phenotypic drug resistance and genotypic mutation patterns of HIV subtypes in Uganda among patients taking antiretroviral medications.
- Characterize evolvement of resistance of ARVs in patients in clinical care.
- Examine emergence and fading of NVP resistance mutations in mothers that have received NVP.
- Determine the prevalence of resistance mutation in mothers and babies who have received NPV.

Genotypic resistance to AZT, 3TC and NVP was commonly observed among ARV experienced participants. Resistance to ddI and D4T was not common. Subtype specificity was not observed in the development of resistance. NVP resistance was detected more frequently in infants than women following NVP prophylaxis with different patterns of

mutation selected in women versus infants. NVP resistance does not persist over time in the absence of drug pressure. Cross-resistance in NRTI was not commonly found.

ARV Drug Resistance in South Africa

Studies are underway to investigate whether failure of anti-retroviral therapy to prevent HIV-1 transmission from mother to child is due to the presence of anti-retroviral drug resistance mutations. In addition, drug resistance is being monitored in individuals exposed to single dose NVP PEP compared to 6 weeks of AZT starting within 72 hours of birth. In addition, the SA government is funding resistance studies at 2 pilot sites where NVP is being implemented, involving 600 mother-infant pairs with 18 months follow-up.

Antiretroviral Drug resistance surveillance projects at CDC in recent infections

CDC ARVDR Surveillance projects focuses on newly diagnosed / newly infected individuals. The US has five branches of the ARVDR component coordinated by the prevention services research branch. They also support projects in several African countries. They also have a new surveillance project in Vietnam, with representative samples of newly diagnosed individuals, as well as individuals treated for 3 years.

Prevalence of ARVDR among the newly diagnosed (transmission of resistance) is a function of many factors affecting the source (partner) population, including:

- Access to care
- How frequently/when physician treats
- Appropriateness of regime
- Regimen outcome – adherence, absorption, trough drug levels
- Success of risk reduction measures
- Relative transmissibility of strains

Sentinel surveillance for variant and resistant strains of HIV, 1998-2000.

- Consenting participants sequentially enrolled in HIV testing sites in 10 cities
- Risk demographic behavioural and clinical information collected
- Blood samples (ACD) – plasma-genotyping
- Phenotyping of strains with mutations of interest
- Serological testing algorithm for recent HIV seroconversions (STARHS)
- Set of mutations used to define ARVDR:IAS December 2001: all Reverse Transcriptase and primary protease mutations. There is a need to set up defined combination mutations, which are considered relevant.

3.4 Elements of ARV Drug Resistance Monitoring in developing a protocol for monitoring ARV;

The following key issues were considered:

What populations are to be monitored and why?
What sampling schemes will be used?
What types of information will be collected from each selected individual?
Which methods will be used?

What QA systems need to be put in place?
Which data management will be used?
How will the tests be interpreted?
What programmatic data need to be collected to facilitate interpretation and utilization of ARV resistance monitoring data?
What are the ethical issues?

The working groups reached consensus on the key issues as follows:

What populations are to be monitored and why?
What sampling schemes will be used?

Type of Population:

- Treatment naive, newly diagnosed infections

Definition: Newly diagnosed HIV infected individuals (with unknown duration of infection).
Sample size: Ideal: 300. Minimum: 150 divided quarterly.
Sampling Scheme: Consecutive patients.
Sampling Frequency: Followed at baseline, then triannually until evidence of resistance (i.e., prevalence greater than 2.5%), at which time followed annually.
Priority Sample Population: Women from one or more antenatal clinics.
Recommended locations of clinics: Regions where ARV are generally available.
Advantage: This will be the group, which could be followed across maximum number of countries. It is also a group that has been standardized.
Outputs: Prevalence and characteristics of transmitted virus.

- Treatment experienced

Definition: HIV infected individuals who are on first-line triple-drug therapy for at least 6-18 months and who have not changed therapy.
Sample size: 150.
Sampling Scheme: Consecutive patients,
Sampling Frequency: Annually
Priority Sample Population: HIV treatment clinics.
Clinics should be selected where ARV is available within regions and where individuals are likely to have future access in the public health care settings.
Recommended Location of Clinics: Clinics treating patients in the context of a well-defined programme.
Advantage: easily reached population.
Outputs: Prevalence of drug resistance among treated populations.
Identify mutations eventually associated with treatment failure.

The above is a recommended minimum patient sample size and selection scheme. If a country has the resources and ability, other populations briefly described in Annex 1 can be utilized.

What are the ethical issues?

Protocols should be reviewed by each country's ethical review board.

The group will develop a protocol for dissemination of sensitive information including data ownership and publication.

What programmatic data need to be collected to facilitate interpretation and utilization of ARV resistance monitoring data?

Aggregate reporting

For each treatment center, or each clinician within the center:

- Number of patients who began ARV treatment this year
- Number of patients who began ARV treatment with standard first line regimens this year (according to country guidelines)

For each center:
Number of months during which adequate supplies of all drugs were available

Additional program elements to be reported if possible:

- Number of patients who began ARV treatment (for reason listed in area guidelines) List each reason and number who began treatment for that reason
- Number of patients on ARV treatment whose regimens were switched during the year
- Number of patients whose regimens were switched who were switched to an appropriate regimen
- Number of patients on ARV treatment at beginning of year
- Number of patients on ARV treatment who picked up all prescriptions during the year

What types of information will be collected from each selected individual?

If reporting on individuals is possible, record information on each individual beginning ARV treatment at baseline, then at six months, then at one year, or at time of blood draw for surveillance program

Information to be collected at baseline (time treatment starts, before treatment starts) for cohort monitoring of programmatic factors:

- Date of birth
- Gender
- Ethnic group (defined locally)
- Place of residence
- Date of HIV diagnosis
- Total lymphocyte count at start of treatment
- Hemoglobin/hematocrit at start of treatment
- Severe symptoms or AIDS-defining conditions at diagnosis (See Appendix)
- Weight at start of treatment
- CD4+ count/ viral load at diagnosis, if available
- CD4+ count/viral load at start of treatment, if available
- List of ARV drugs prescribed and date drugs first taken
- Reason for beginning ARV treatment

Then every six months:

- Changes in regimen made in past six months (List drugs, date, reason)
- Toxicity rating
- New occurrences of severe symptoms/AIDS-defining conditions during the past six months on treatment
- How many prescriptions for ARV written in past six months? How many prescriptions picked up one or more days late? How many prescriptions not picked up at all?
- Minimum adherence measure: has patient not taken one or more drugs in regimen for ≥ one week during the past six months? (list drugs not taken for ≥ one week)
- Diarrhea for more than one month for past six months
- Weight
- [Measures of drug absorption or trough levels, if performed for other reasons]
- Known behaviors associated with risk of HIV transmission for past six months

Essential data items for both newly diagnosed, ARV-drug-naïve patients and ARV-treated patients (E)

- Gender (E=essential)
- Date of birth or age (E)
- Date of specimen collection (E)
- Group definition – population group such as TB pts, pregnant women (E)
- Area of residence (E)
- Facility at which blood was drawn (E)

Additional data items for ARV-treated patients (A)
In addition to data items listed for both groups:

- Regimen (List of drugs being taken) at blood collection (E)
  - List name and dosage of each drug, and whether generic or proprietary
- Treatment facility (E)
- Date of last drug dose (E) – patient must be currently taking his/her regimen – exclude if > 1 week since last dose taken
- Date first ARV treatment began – (E) for individuals on their first regimen; (D=desirable) for others

Desirable data items for ARV-treated patients (D)

- Initial regimen (D)
  - List name and dosage of each drug, and whether generic or proprietary
- MTCT regimen taken previously (D)
  - List name and dosage of each drug, and whether generic or proprietary
- How many drug doses missed in the last month of treatment? (D)
- Ever stopped taking one or more ARV drugs for more than one month? (D)
- New occurrences of AIDS-defining conditions in last six months (D)
  - Form should include a list to be ticked
- Diarrhea for more than one month in past six months? (D)
- Weight at start of ARV treatment (D)
- Weight at blood collection (D)

- **Treatment naive, newly infected (< 6 months)**

- Provide the best estimates of trends in transmission of drug-resistant virus
- What will be the case definition of newly infected?
    - seronegative within previous 6 months
    - p24 positive or RNA positive with antibody negative
    - evolving Western Blot and detectable HIV RNA (has limitations),
    - detuned ELISA (has limitations)

- Provide clade specific baseline data including accessory polymorphisms

- **Treatment naive, chronic infection (newly diagnosed)**

HIV infected individuals, no history of ARV therapy, and unknown duration of infection. This will be the group, which could be followed across maximum number of countries.

- Provide clade specific baselineline data including accessory polymorphisms,
- Possible indicators of primary drug resistance transmission

- **Treatment experienced**

HIV infected individuals who have been on therapy for 6 –18 months and who have not changed therapy.

- To help countries make appropriate decisions in selecting second line regimes
- To provide data to be used in program management.

Surveillance data will provide trends of drug resistance and
to define subtype specific mutations associated with treatment failure

- Short-course treatment (MTCT)

- Women and children who have received PMTCT short course therapy.

- Emergence of resistance and persistence of resistant mutations associated with MTCT

How will the tests be interpreted?

The tests will be interpreted using the Stanford database

Which methods will be used?

Specimens will be collected from eligible patients as follows:

- 2x 10ml blood in EDTA tubes or CPT.
- Specimens will be shipped to the local laboratory within 4-6 hours.
- Lymphocytes and plasma will be stored at 20°C according to established procedures.
- A minimum of 4 aliquots of cells and 10 x 1 ml aliquots of plasma will be stored at –70°C until required for testing.

- Genotype(E)- 1000 nucleotides, 300 protease and 700 RT
- RNA genotyping(E)

- Phenotype(A)

What Quality assurance systems need to be put in place?

Initially to exchange samples (that have been genotyped before) between laboratories to test the different genotyping systems. Six samples were recommended, two with no mutations, two with low viral loads, two with high viral loads. One of the sites will prepare a supply of spiked plasma containing known HIV-1 subtype A,C,D and AG genotype with specific resistance mutations to be used by controls for each assay at each site. These spiked plasma specimens will be run as controls with every batch of 10 specimens to be sequenced in order to provide extensive information on reproducibility and to ensure accuracy of data. In addition a series of titrations of spiked specimens will be sequenced in order to determine the threshold of each assay.

Which data management system will be used?

The following information for each test carried out on each specimen will be recorded:

- Complete aligned sequence data, identification of resistance mutations, a summary of drug resistance (interpretation of resistance mutations), phenotypic resistance information (if done).
- Reproducibility assessment for each commercial product will be carried out based on

    ✓ Complete sequence data
    ✓ Identification of resistance mutations
    ✓ Interpretation of resistance mutations (complete sequencing data may not match but interpretations may be the same)

Reproducibility for all 3 parameters will be calculated for testing done within the same site and between sites.
Sensitivity for each assay will be calculated as the proportion of true mutations the procedure correctly identifies. The mutation is known to exist because it has been detected in sequences derived from cloned PCR products or the phenotypic assay.
Specificity for each assay will be calculated as the rate of true wild type codons correctly identified compared to sequences derived from cloned PCR products and/or the phenotypic test.
Overall agreement between assays (sequences derived from cloned PCR products versus each assay) will based on

1. complete sequence data
2. detection of resistance conferring mutations
3. detection of other detection polymorphisms
4. interpretation of resistance mutations

Where possible, the presentation of data will be to sort the information according to the specific drug. i.e. for each drug the relative sensitivity and specificity of the assays will be compared.

3.5 Recommendations and Next Stages:

The following were the key recommendations of the workshop:

- **Recommendations:**

1. To initiate the validation process for the different genotyping methods utilized by the participating laboratories.

2. WHO to assist with evaluating existing QA programs and their adaptation to meet the specific goals of this initiative.

3. WHO to negotiate with companies for free/subsidized kits and / or equipment to strengthen capacity at the laboratory level.

4. To create mechanisms to facilitate the dissemination of surveillance models, methodologies based on sound scientific principles. To improve, strengthen and support other surveillance efforts at country level.

5. To develop mechanisms to support/develop the implementation of surveillance in other countries not currently participating.

6. Hold meetings, at intervals to be established in the future, in order to assess progress, identify strengths and weaknesses and compile a document summarizing "lessons learned" during the implementation process.

7. Establish mechanisms in order to provide feedback to clinicians.

8. To establish ways in which to link this program with existing drug access programs.

9. To assist in the development of country level databases in order to integrate and facilitate data exchange among participating laboratories.

10. To explore funding opportunities and possibilities for linking this program with existing programs supported through the Global Funds and Accelerated Access Initiatives.

11. Obtain feedback on the proposed surveillance program as a whole, on the data collection tools (questionnaire, forms, etc...) prior to finalizing the drafts and beginning program implementation, from participating members and major stake-holders.

12. The task-force members will strive to identify funding opportunities to support this initiative.

The following were identified as the follow–up actions:

- A report will be sent to the participants summarizing the proceedings of meeting.
- To develop country level protocols and budgets.
- To define the roles of the different participants (laboratories and organizations).

- To draw on existing WHO guidelines regarding the ethical conduct of studies and to establish mechanisms for data handling, sharing, dissemination and publication.
- WHO will establish links with Ministries of Health, and other country level stake-holders in order to promote the implementation of the surveillance protocol.
- To finalize the protocol.

4.0 CLOSING:

The workshop was closed by Dr G.M. Gershy-Damet, Regional officer for HIV laboratory , WHO/AFRO, on behalf of the Regional Director.

Annexe 1. Definitions of Populations for Surveillance

Population Group	Advantages	Disadvantages
Pregnant Women and mother/child clinics e.g. vaccination clinics	• Easy to enroll • Critical data for MTCT prevention • With repeated measures can get trends and reduce problem or less representative	• Less representative • Limited information?
Facility-Based individuals on treatment	• Easy to enroll • Useful for trends over time which will reduce representation problems	• Not representative • Careful selection • Possible change in resistance pattern with duration of infection
Newly Diagnosed (VCT centers, TB center)	• Easy to enroll • More representative of targeted treatment group	
Newly Infected	• Best information for choosing ARV therapy • Useful for trends over time	• Difficult to identify and enroll • Poorly representative of all HIV- infected
Convenience Sample from General Population	• Easiest to enroll	• Difficult to interpret results
Blood Bank	• Ease of sampling	• Limited data
Military recruits, large companies e.g. mines	• Ease of sampling • Ease of follow-up	• Access • Ethical issues

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